PANEL PROCEEDINGS SERIES

BIOCHEMICAL INDICATORS OF RADIATION INJURY IN MAN

PROCEEDINGS OF A SCIENTIFIC MEETING
ON BIOCHEMICAL INDICATORS OF RADIATION INJURY IN MAN
JOINTLY ORGANIZED BY THE
INTERNATIONAL ATOMIC ENERGY AGENCY AND
THE WORLD HEALTH ORGANIZATION
AND HELD IN PARIS-LE VESINET, FRANCE
22—26 JUNE 1970

INTERNATIONAL ATOMIC ENERGY AGENCY
VIENNA, 1971

PANEL PROCEEDINGS SERIES

BIOCHEMICAL INDICATORS OF RADIATION INJURY IN MAN

PROCEEDINGS OF A SCIENTIFIC MEETING
ON BIOCHEMICAL INDICATORS OF RADIATION INJURY IN MAN
JOINTLY ORGANIZED BY THE
INTERNATIONAL ATOMIC ENERGY AGENCY AND
THE WORLD HEALTH ORGANIZATION
AND HELD IN PARIS-LE VESINET, FRANCE
22—26 JUNE 1970

INTERNATIONAL ATOMIC ENERGY AGENCY
VIENNA, 1971

BIOCHEMICAL INDICATORS OF RADIATION INJURY IN MAN
IAEA, VIENNA, 1971
STI/PUB/280

Printed by the IAEA in Austria
March 1971

BIOCHEMICAL INDICATORS OF RADIATION INJURY IN MAN

FOREWORD

After an organism has suffered a radiation insult, knowledge of the dose and localization of the exposure is of the greatest importance for the treatment of any radiation damage. Supplementary to the information obtained from physical dosimetry, data obtained by biochemical indicators can, on the basis of metabolic changes in the irradiated organism, help in making early diagnosis, in assessing the extent of the radiation injury, and making a prognosis. Biochemical tests under optimal conditions would not depend on the quality and distribution of the dose in the body and would also reflect the sensitivity of the individual organisms.

The International Atomic Energy Agency and the World Health Organization convened a joint scientific meeting on Biochemical Indicators of Radiation Injury in Man in Paris-Le Vésinet, France, from 22 to 26 June 1970. The main purpose of the meeting was to discuss recent problems in determining which biochemical and metabolic changes occurring in irradiated organisms could be used as indicators of radiation injury and its extent, and could thus be of help in planning the proper treatment of the injured persons. During the meeting the results obtained with various biochemical indicators, and experimental techniques and laboratory methods used in this field, were evaluated and compared.

Both research workers and clinicians were invited to participate at the meeting. They discussed the possible value of several tests, used successfully in experimental animals, for clinical application; ways of standardizing suitable tests; and mutual collaboration between laboratories and clinics. The outcome of their discussions is summarized in the conclusions and recommendations which are included in these Proceedings together with the papers presented.

The meeting took place at the Service Central de Protection contre les Rayonnements Ionisants du Ministère de la Santé Publique et de la Sécurité Sociale in Paris-Le Vésinet. The organizers wish to express their great appreciation of the help given by Professor P. Pellerin, Director of this Institute, and his staff, as well as by the staff of the Commissariat à l'Energie Atomique, in arranging the meeting.

此为试读,需要完整PDF请访问: www.ertongbook.com

CONTENTS

CRITERIA FOR THE EVALUATION AND SELECTION OF RADIATION-INDUCED METABOLIC CHANGES AS BIOCHEMICAL INDICATORS OF RADIATION DAMAGE*

K. I. ALTMAN
Departments of Experimental Radiology,
Radiation Biology, Biophysics and Biochemistry,
The University of Rochester,
School of Medicine and Dentistry,
Rochester, N.Y.,
United States of America

Abstract

CRITERIA FOR THE EVALUATION AND SELECTION OF RADIATION-INDUCED METABOLIC CHANGES AS BIOCHEMICAL INDICATORS OF RADIATION DAMAGE.

There are several reasons which prompt a search for suitable biochemical indicators of radiation damage in man. Perhaps the most compelling of these reasons is the urgent need for estimates of exposure doses in cases of accidental exposures of human subjects to ionizing radiations under conditions which preclude a reliable assessment of the exposure dose by the usual physical means. At worst, a biochemical estimate of the dose would provide an independent means of obtaining information otherwise based solely on physical considerations and assumptions. In addition, a biochemical estimate of radiation injury may also, under ideal circumstances, serve as a guide to the attending physician in chosing the type of therapy most efficacious and least likely to lead to complications in the near as well as more distant future. The availability of biochemical indicators capable of revealing with some degree of accuracy the impairment of function of a particular organ would be a helpful adjunct in making decisions concerning the therapeutic approach to be adopted. The latter aspect would be of considerable interest in acute, accidental radiation exposures since under these circumstances radiation exposures are frequently of the partial-body type. An estimate of radiation injury by means of biochemical indicators should also prove useful in cases of protracted or chronic exposures to radiation, the source of which may be either external or internal. The use of biochemical indicators under these conditions of radiation exposure may, in general, aid "case-finding" efforts and, in a more specific way, may help in pin-pointing discrete organ dysfunctions. In evaluating the suitability of radiation-induced metabolic changes for application as biochemical indicators of radiation damage, the following general criteria may be set forth: (1) the biochemical response to irradiation must be dose-dependent within a certain, sufficiently wide range in order to be useful; (2) the sensitivity of the indicator should be high in terms of units of response per R exposed to; (3) the detectability of the biochemical response in relation to the time of exposure should, under ideal conditions, be maximal at a single time point during the post-irradiation period and this time point should not vary with the radiation dose; (4) the biochemical procedure for detecting the radiation response should be rapid, simple, and capable of execution in clinical laboratories not necessarily equipped with sophisticated apparatus; (5) the sample to be examined should be readily biopsied without endangering the recovery of the patient (the preferred method is the one which can be repeated several times, i.e. with which samples from the same patient can be

* This paper is based, in part, on work performed under contract with the U.S. Atomic Energy Commission at the University of Rochester Atomic Energy Project and has been assigned Report No. UR 49-1333.

obtained repeatedly with impunity); (6) the indicator selected should not suffer from interference by metabolic changes which are related to disease processes not related to the sequelae of exposure to ionizing radiations, e.g. malignancies, intercurrent infections, etc. Since many of the conceivable biochemical indicators depend upon contributions by various organs and thus possess little organ specificity and since other possible indicator systems represent indirect effects mediated by adrenal, pituitary, and other hormones, it seems realistic to assume that no single biochemical indicator will be satisfory in any one situation, but that, instead, multiple biochemical indicators will need to be resorted to in order to explore all possible aspects of radiation damage. Thus, indicators will be needed which are applicable at various dose levels and times after exposure. Furthermore, the ideal indicator system should be applicable after total- as well as partial-body irradiation, a special case of which would be a completely organ-specific indicator.

It seems worthwhile to begin my paper by posing a basic question, namely: Why are we interested in biochemical indicators of radiation damage? Since this question touches on the motivating reasons for holding a meeting such as this one, it seems to me to be fundamental to the subject at hand. Several reasons for our interest in biochemical indicators can be enumerated:

1. In which areas and under which circumstances can the application of biochemical indicators be envisaged? I am referring here to the realm of practical applications which I consider the basic theme of my paper, particularly as these applications benefit man.
2. Are the metabolic responses to an exposure to ionizing radiations, either at sub-lethal or at lethal-dose level, sufficiently specific to justify the hope that they can serve as the basis for developing reliable and quantitative biochemical methods for assessing radiation damage in man? And, as a corollary, let us ask whether such specificity is obtainable, in practice: at what level do metabolic responses resulting from, as an example, intercurrent diseases, interfere with our interpretation of those similar effects from ionizing irradiation, and becloud an accurate assessment of the latter?
3. Is there a reasonable chance of discovering biochemical indicators which will be capable of revealing in a quantitative way the extent, if not the anatomical location, of radiation damage in relation to the absorbed radiation dose?
4. What is the present "state of the art" in the field of biochemical indicators of radiation damage and what are the expectations for the immediate and long-range future?
5. Which of the pertinent areas of metabolism are most likely to yield useful results in terms of practical applications to human situations?

Although the preceding considerations emphasize the practical aspects of the problem, and are aimed at the prospects for application to human situations, I do not wish to leave the impression that the search for biochemical indicators of radiation damage will not be rewarded by yielding certain "hidden benefits", i.e. new insights into the metabolic functions of man and animal exposed to ionizing radiations, especially in the area of intermediary metabolism. Novel findings regarding human intermediary metabolism may subsequently contribute, by means of "feed-back" processes, to the refinement of existing biochemical indicators or to a discovery of new approaches to the problem.

To return now to an examination of and, if possible, to a reply to the questions raised above, I will proceed by taking up these questions in their numerical order. As to question 1, the following areas seem appropriate for an application of the indicators in question to man:

a. Accidental exposures to ionizing radiations, either at sub-lethal or lethal-dose levels:

(i) Exposure to an external source of radiation.

(ii) Exposures to an internal source of radiation, i.e. to internal emitters. This category seems germane here if one considers situations of suspected intake of radioactive materials, which cannot be subjected to satisfactory physical dosimetry or for which dose calculations based on physical considerations are subject to such large uncertainty factors as to make this type of dosimetry impractical.

b. Therapeutic partial- or total-body exposures to ionizing radiations for the treatment of malignancies of various types may be subdivided into several categories:

(i) Exposures to external radiation only.

(ii) Exposures to internal radiations only, e.g. radium, ^{198}Au, etc.

(iii) Mixed, but not necessarily simultaneous exposures combining (i) and (ii).

Among the circumstances under which applications of biochemical indicators seem suitable are the following:

(a) In the cases of accidental exposures, an uncertainty of the radiation dose received may be at least partially eliminated if a biochemical indicator or indicators can be employed. Under these circumstances biochemical indicators may aid in arriving at a decision whether or not certain types of treatment are indicated and, if so, which particular ones. If biochemical indicators were available which are capable of specifically reflecting radiation damage in a particular organ, it may become possible to estimate the distribution of the dose of radiation received at different anatomical sites. This, in turn, would further assist the clinical management of the case by providing a basis for deciding on the nature of the supportive therapy to be used and the prognosis for the case in question.

(b) Accidental intake of radioactive materials of known or unknown chemical identity, fall-out subsequent to nuclear explosions, and industrial or laboratory accidents constitute examples of circumstances under which knowledge pertaining to the site and extent of tissue damage would be valuable. In addition, biochemical indicators would be useful as monitors of procedures designed to delocalize internal emitters deposited in tissues. It is conceivable that the response of certain types of indicators may be correlated with the biological half-life of the emitter and provide estimates of the cumulative dose absorbed.

(c) In the case of therapeutic irradiations, a most useful type of test, applicable under circumstances of massive tumour therapy, would be one which

is capable of reflecting, in some way, the response or lack of response of the tumour to irradiation. Because of the complexities of the cell populations in the tumour per se as well as variability of the vascular, and, hence, oxygen supply to the tumour, such a test has not yet been developed and perhaps will not be developed within the foreseeable future. A possible exception are neoplasms which are characterized by special functional capabilities, e.g. certain tumours of the skin.

The study of biochemical indicators in radiation-therapy patients provides what is possibly the sole practicable opportunity for exploring metabolic responses to ionizing radiations in man, although always with the qualification that the tumour patient is not a "normal" man and that the presence of a tumour and the existence of a metabolic interplay between tumour and host may decisively alter metabolic responses to the exposure to ionizing radiations. In man, and especially in the radiation-therapy patient, estimates of the effects of internal sources of radiation may well constitute the most promising controlled test system for the applicability of biochemical indicators, provided that the indicator to be tested is sufficiently sensitive to register a response to the irradiation of a relatively small tissue volume. Examples which illustrate this point are available, for example, from studies involving intracavitary radioactive gold therapy [1].

As to the second question which I raised earlier concerning the specificity of metabolic responses to ionizing radiations, only a qualified answer seems meaningful. Viewed superficially, the response to ionizing radiations bears all of the earmarks of the general response to noxious agents of a great variety of different types, e.g. trauma of various origin and other stress-producing circumstances. However, this superficial impression is tempered by the knowledge that, among the important sequelae of exposure to ionizing radiations, cell destruction and subsequent in-vivo "autolysis" in radiosensitive organs create a kaleidoscopic picture of metabolic changes. As a result of the metabolic changes at the cellular and sub-cellular levels, a multitude of tissue constituents are liberated from cells and cell debris and find their way into body fluids, where these constituents, be they macromolecular in nature or of low molecular weight, can be sampled.

As to the extent to which intercurrent disease or medications may constitute complicating factors, may totally obscure results, or may introduce uncertainty factors which might make interpretation of findings difficult or highly ambiguous, this differs widely from case to case.

Whether or not specificity should be considered an important feature in evaluating the suitability of a metabolic reaction for application as the biochemical indicator of radiation damage, a decision must depend upon the presence of interfering intercurrent disease, the nutritional factors involved, the nature of the injury in terms of the anatomical sites involved and, perhaps most importantly, the number of biochemical indicators which can be employed usefully in any individual case. The deployment of a battery of biochemical indicators, each testing a different metabolic parameter, appears to me a matter of utmost importance since no single biochemical indicator is likely to reflect

此为试读,需要完整PDF请访问: www.ertongbook.com

adequately the extent and anatomical location of radiation damage which has resulted in the impairment of function of several organs. This point is well documented by past experience gathered in the course of the study of human radiation-accident cases. However, since the modus operandi of many biochemical indicators is based on the radiation-induced destruction of cells and the subsequent degradation of macromolecules and since there exist distinct differences in the temporal response of different organs and a graded scale of radiosensitivity of the cell populations inhabiting these organs, it is conceivable that the same biochemical indicator may be useful in differentially detecting radiation damage in different organs at different times after exposure to ionizing radiations. The desirability of employing organ-specific indicators, alluded to earlier, has its place in this context in that application of organ-specific tests would, by necessity, involve application of multiple indicators.

Since metabolic changes must be viewed within the overall perspective of the total organism, some metabolic changes induced by irradiation may not be reflected under in-vivo conditions although one would be inclined to predict, on the basis of in-vitro studies, that certain metabolic changes should become manifest after exposure. Various reasons might be advanced in order to explain this occurrence; foremost among these ranks the possibility that an accumulation of radiation-induced metabolites may be counteracted by excessive utilization or transformation and subsequent distribution and storage in other metabolic compartments of the body.

If the nutritional status of the individual is of such a nature that metabolic consequences are to be expected, a high degree of specificity of the metabolic reaction chosen as the basis for the biochemical indicator would be desirable. Even in the face of such adversity a given metabolic reaction may evolve as a useful indicator, as shown by Fig. 1 in the case of radiation-induced

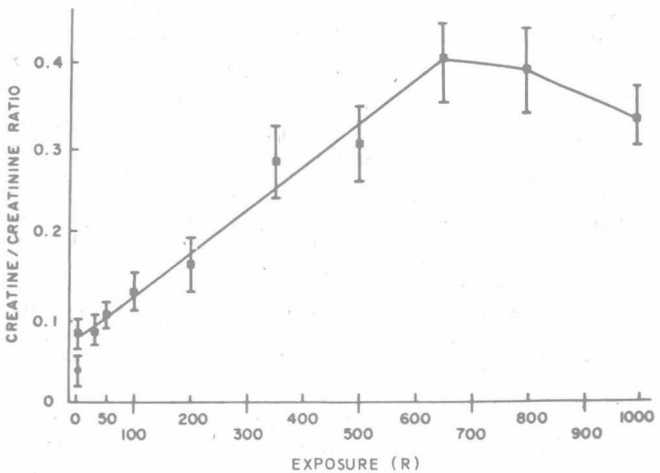

Fig. 1. The dose dependency of radiation-induced creatinuria in the rat after a single total-body X-irradiation [3].

creatinuria [2—4] which also can be caused by a reduction of the daily food intake, immobilization, etc. However, the excretion of creatine after irradiation is considerably higher than that found in starved or immobilized individuals. It thus seems that a certain degree of non-specificity does not necessarily detract from the usefulness of a metabolic reaction and, therefore, in my opinion, radiation specificity does not constitute an obligatory requirement for a useful biochemical indicator.

One of the challenging aspects in the field of biochemical indicators, at least from my point of view, is the possibility of assessing radiation injury at discreet anatomical sites by means of sampling normal and abnormal metabolites, which reflect metabolic changes, in body fluids or bioptic materials. The metabolites referred to in this context should be characteristic of a specific organ or tissue and reflect its unique functional capacities. That such a possibility is not merely a biochemists's dream (or nightmare?) is documented by the existence of a limited number of metabolic reactions which have served as biochemical indicators with tissue specificity, e.g. the urinary excretion of hydroxyproline and pyrrole-2-carboxylic acid which represent the end products of collagen catabolism and, therefore, reflect a unique facet of connective tissue metabolism [5]. Although present-day knowledge of collagen metabolism has been enlarged predominantly on the biosynthetic side with corresponding neglect of the catabolic aspect, available data suggest that the study of collagen catabolism, as sampled via its products appearing in the urine, is still a fruitful undertaking.

Although one may conjure up many tests for excessive tissue breakdown after irradiation, all of which would be capable of detecting radiation damage in a qualitative sense, it is a task of a considerably greater magnitude to quantitate this damage in terms of the radiation dose absorbed or in terms of some other unit of measurement (survival). In this domain relatively little has been achieved. The criteria applied to evaluate relationships have been largely based on the dose dependency of the metabolic change considered. Linearity of a plot of dose versus metabolic change over a wide range of 1000—2000 R is interpreted to mean that the indicator is a useful one, especially if the slope of the line is steep. The steepness of the slope of this line indicates that the sensitivity of the indicator is within a usable range.

A desirable attribute of a biochemical indicator in connection with the foregoing considerations is the ability to detect damage because of exposure to ionizing radiations at a level at which clinical symptoms are not yet apparent, i.e. at a sub-clinical level. This attribute is closely related to the sensitivity of the indicator and its presence depends on a prudent choice of the metabolic reaction which, in turn, would have to be capable of registering subtle changes of a metabolic nature. Such metabolic reactions can be found and an example of a biological test system may be cited by recalling the work on ^{59}Fe-incorporation in circulating red blood cells, an indicator for which initial claims for sensitivity at exposure levels of as little as 25 R were made [6] (see Fig. 2). A more realistic appraisal, at least in our experience, is 75 R as the lowest detectable dose by this method. This method does, in fact, detect sub-

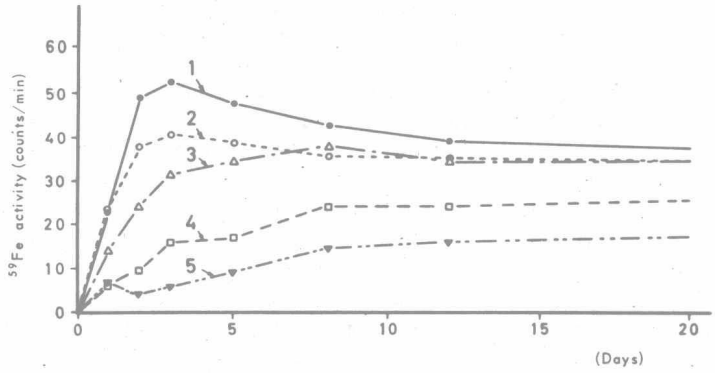

Fig. 2. The uptake of ^{59}Fe by rat erythrocytes after a single total-body exposure to X-rays; ^{59}Fe was injected at the time of irradiation [6].

clinical damage because at these low levels of exposure to X-irradiation there appears to be no clinical evidence of haematopoietic damage (single dose). Relatively little information regarding the human subject is available with respect to this type of test and those investigations which have been published are to a large extent difficult to interpret. Parenthetically, it should be mentioned that the use of a biological test system such as the one just mentioned might, on first sight, be deemed as contra-indicated, inasmuch as the use of an isotopic tracer as a diagnostic tool in a person already exposed to excessive doses of ionizing radiations may cause the attending physician to hesitate. However, under proper management and the use of only a tracer dose of the respective isotope, this procedure should not have any untoward effects, since the dose of isotopic tracer would be extremely small in relation to the accidental radiation received.

In this same context and also in reference to the earlier mention of temporal aspects, I may cite another desirable attribute of the metabolic reaction which is to serve as biochemical indicator, namely, that the reaction should, if possible, be detectable early, i.e. during the first two days of the post-irradiation period. This feature would be of particular importance in those situations which require the rendering of vital decisions regarding the clinical management very early in the post-irradiation course. It is also known that the maximal temporal response of a biochemical indicator may change as a function of dose. This point is well illustrated in the case of creatinuria which reaches maximal levels at different times after exposure depending on the dose of radiation [3] (cf. also Fig. 1).

As to the present "state of the art" concerning the use of biochemical indicators of radiation damage, one cannot escape the conclusion that this field is still in a state of infancy and that striking developments are not to be expected in the "immediate future", unless new advances in various pertinent areas of metabolic function are forthcoming. This statement is based on the conviction that the application of metabolic reactions as biochemical indicators is very often given its impetus by current advances in our knowledge about

metabolism in general. The long-range prospects are, I believe, somewhat brighter since the possibility of developing satisfactory organ-specific indicators seems plausible.

Concerning the final question posed, namely, where among the many metabolic reactions should one search for the ideal biochemical indicators that will serve as biological dosimeters as well as indicators of radiation damage, no simple reply can be given. Several factors are to be considered in arriving at a meaningful postulate. The metabolic reactions chosen should have the following characteristics:

(a) The metabolic reactions should be capable of being sampled in body fluids or in tissues which can be biopsied easily from the patient's point of view and constitute no hazard to the patient. This confines exploration to three main sources for sampling: blood, urine and expired air. Minor sources for sampling could be: spinal fluid and certain organs from which samples can be obtained by punch biopsy. I feel impelled to comment briefly on the use of expired air samples in connection with biochemical indicators, since this is an area which is still very much in the "foetal" stage of development. However, examination of expired air by means of mass spectrometry could yield interesting results, particularly since this technique would permit repeated sampling on an almost continuous basis. Of the volatile compounds present in human breath, several are of interest from a metabolic point of view and show that this approach may be rewarding.

(b) Since it seems mandatory that the biochemical indicator yield unequivocal information as to the existence and, if possible, the extent of radiation damage and the anatomical sites of damage, the choice of metabolic reactions is limited indeed when taken together with the restraints imposed on such a choice, mentioned earlier here. By and large, the specification of unequivocal results will be satisfied best by applying metabolic reactions which, in the irradiated organism, result in the accumulation of metabolites in amounts substantially exceeding those normally present. At this point, I must interject a strictly technical consideration of an analytical-chemical nature: the method employed in assaying the concentration or amount of the metabolite in question must be so sensitive, specific, and reliable as to make possible unequivocal results. In addition, the chemical procedure should preferably be sufficiently simple to permit its use in a moderately well equipped and staffed laboratory.

(c) As alluded to earlier, it is my opinion that a single biochemical indicator test will not adequately reveal multiple injurious effects of exposure to ionizing radiations. For this reason the application of a battery of tests of biochemical indicators is envisaged. Ideally, this battery of tests should contain two types of indicator tests: (1) those tests which complement each other, and (2) those tests which should serve to confirm others; tests which test the same metabolic function, but which are based on a different metabolic reaction. This takes us back full circle to organ-specific indicators!

REFERENCES

[1] SCHREIER, K., personal communication.
[2] GERBER, G.B., GERBER, G., ALTMAN, K.I., HEMPELMANN, L.H., Int. J. Radiat. Biol. 3 (1961) 17.
[3] GERBER, G.B., GERTLER, P., ALTMAN, K.I., HEMPELMANN, L.H., Radiat. Res. 15 (1961) 307.
[4] GERBER, G.B., GERBER, G., ALTMAN, K.I., Proc. Soc. expl. Biol. Med. 110 (1962) 797.
[5] KONNO, K., TRAELNES, K.R., ALTMAN, K.I., Int. J. Radiat. Biol. 6 (1964) 367.
[6] HENNESSEE, T.G., HUFF, R.L., Proc. Soc. expl. Biol. Med. 73 (1950) 436.

此为试读,需要完整PDF请访问: www.ertongbook.com